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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,770	BORNSTEIN ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28 and 31-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28, and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Office Action is a response to Applicants Amendment and Remarks, filed January 23, 2004.

Claims 1-27, 29, and 30 have been canceled. New claims 33-36 are acknowledged. Claims 28 and 32 have been amended.

Claims 28, and 31-36 are pending in the instant application.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7 and 10-18 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to (1) reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and (2) enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **These rejections are moot** in view of Applicants Amendment to cancel claims 1-7 and 10-18, filed January 23, 2004.

Claim Rejections - 35 USC § 102

Claims 1 and 11 were rejected under 35 U.S.C. 102(b) as being anticipated by Liaw et al. (Journal of Clinical Investigation, 1998 Vol. 101:1468-1478). **This rejection is moot** in view of Applicants Amendment to cancel claims 1 and 11, filed January 23, 2004.

Claims 1, 11, 12 and 15 were rejected under 35 U.S.C. 102(e) as being anticipated by Peterson et al. [WO 99/33415]. **This rejection is moot** in view of Applicants Amendment to cancel claims 1, 11, 12 and 15, filed January 23, 2004.

Claims 1-5, 10, 12, 28 and 29 were rejected under 35 U.S.C. 102(e) as being anticipated by Detmar et al. [WO 00/57899]. **This rejection is moot against claims 1-5, 10, and 12** in view of Applicants Amendment to cancel claims 1-5, 10, and 12. **This rejection is withdrawn against claims 28 and 29** in view of Applicants arguments, filed January 23, 2004. Specifically, the Examiner agrees that the Detmar et al. [WO 00/57899] international application does not have a Section 102(e) date as set forth in MPEP §706.02(f)(l).

Claim Rejections - 35 USC § 112

Claims 28-32 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is withdrawn** in view of Applicants Amendment to the claim to remove osteopontin and its use in the practice of the present invention, filed January 23, 2004.

Applicants Amendment necessitated the new grounds of rejection presented as follows:

Claim Rejections - 35 USC § 102

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 28 is rejected under 35 U.S.C. 102(e) as being anticipated by Streit et al. [U.S. Publication No: 2002/0119921].

Claims 28 is drawn to a method for decreasing the biological activity of thrombospondin 2 in an animal, the method comprising the administration of an antisense thrombospondin 2 nucleic acid molecule that hybridizes to a nucleic acid of SEQ ID NO:3.

Streit et al. disclose a method of decreasing thrombospondin 2 (TSP-2) activity by administering, antisense thrombospondin 2 nucleic acid molecules, a TSP-2 antisense or TSP-2 ribozyme, that binds to cellular TSP-2 mRNA and inhibits (decreases) expression of the protein (see page 5 [0049]). Streit et al. further disclose the level of TSP-2 activity is decreased by intravenously administering a TSP-2 antisense or TSP-2 ribozyme (see page 5 [0050]). Streit et al. further disclose the method of modulating thrombospondin 2 (TSP-2) activity by administering a TSP-2 antisense or TSP-2 ribozyme that binds to cellular TSP-2 mRNA and inhibits (decreases) expression of the protein is performed *in vivo* (see page 5 [0051]). Streit et al. further disclose the nucleotide sequence of TSP-2 (see Streit et al. SEQ ID NO. 1) and the amino acid sequence of TSP-2 (see Streit et al SEQ ID NO. 2). The nucleotide and amino acid sequences of Streit et al. are identical to SEQ ID NOs. 3 and 4 of the instant invention,

respectively. Note also MPEP 2112.01 that states, "if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present."

Therefore, Streit et al. anticipate the instant invention.

It is noted that a similar rejection was made of record in a previous Office Action, filed January 31, 2003 (see page 14).

In response to this rejection, Applicants argued that the Streit et al. patent application was field on March 30, 2001, and claims benefit of priority from US Application No. 09/536,087, filed March 24, 2000, and from US Provisional Application No. 60/127,221, filed March 31, 1999. Applicants contend that the effective date of the Streit et al. application under 35 U.S.C. §102(e) is the filing date of the earliest filed of the foregoing applications which discloses a method of modulating thrombospondin 2 activity by administering a thrombospondin 2 antisense or thrombospondin 2 ribozyme that binds to cellular thrombospondin 2 mRNA and inhibits expression of the protein. Applicants argue that the present application claims the benefit of priority of US Provision Patent Application No. 60/222,071, filed August 1, 2000. Applicants argue that if the portion of the Streit et al. published patent application that discloses a method of modulating thrombospondin 2 activity by administering a thrombospondin 2 antisense or thrombospondin 2 ribozyme that binds to cellular thrombospondin 2 mRNA and inhibits expression of the protein is later than August 1, 2000 then that portion of the Streit et al. published patent application is not prior art with respect to the present application.

Applicants arguments have been reconsidered and the Examiner agrees that if the portion of the Streit et al. published patent application that discloses a method of modulating thrombospondin 2 activity by administering a thrombospondin 2 antisense or thrombospondin 2

ribozyme that binds to cellular thrombospondin 2 mRNA and inhibits expression of the protein is later than August 1, 2000, then that portion of the Streit et al. published patent application is not prior art with respect to the present application. However, the portion of the Streit et al. published patent application that discloses a method of modulating thrombospondin 2 activity by administering a thrombospondin 2 antisense or thrombospondin 2 ribozyme that binds to cellular thrombospondin 2 mRNA and inhibits expression of the protein is **not** later than August 1, 2000. In fact, as Applicants have pointed out, the portion from which the published patent application relies is the US Provisional Application No. 60/127,221, filed March 31, 1999. Therefore, since the earliest priority date of the instant application is August 1, 2000, and the earliest filing date of the Streit et al. published patent application is March 31, 1999, Streit et al. is prior art against the instant application.

Claims 28 and 31-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing the amount or biological activity of thrombospondin 2 in an animal, said method comprising the step of locally introducing into said animal a medical device comprising an antisense thrombospondin 2 consisting of a nucleic acid antisense nucleic acid that hybridizes to SEQ ID NO:3, does not reasonably provide enablement for a method of decreasing the amount or biological activity of thrombospondin 2 in an animal, said method comprising the step of introducing into said animal a structure comprising an antisense thrombospondin 2 consisting of a nucleic acid antisense nucleic acid that hybridizes to SEQ ID NO:3. The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 28 is drawn to a method of decreasing the amount or biological activity of thrombospondin 2 in an animal, said method comprising the step of introducing into said animal a structure comprising an antisense thrombospondin 2 consisting of a nucleic acid antisense nucleic acid that hybridizes to SEQ ID NO:3. Claims 31-36 are dependent on claim 28 and include all the limitations of claim 28, with the further limitations, wherein the structure is a medical device; wherein the medical device is selected from the group consisting of a vascular graft, a vascular stent, an artificial blood vessel, an artificial bone joint, a biosensor, and a percutaneous device; wherein the antisense thrombospondin 2 nucleic acid molecule hybridizes under conditions of 5 X SSC at 65°C; wherein the antisense thrombospondin 2 nucleic acid molecule is at least 90% identical to the complement of the nucleic acid molecule of SEQ ID NO:3; and wherein the animal is a human.

The instant invention specification provides methodologies for locally delivering antisense thrombospondin 2 nucleic acid molecules to a mammalian subject, by incorporating an antisense nucleic acid molecule into the surface layer of an implanted collagen matrix device and improving vascularization of the foreign bodies that forms around the implanted device (see Examples 1 and 2). However, the claims are so broad to encompass a method of decreasing the amount or biological activity of thrombospondin 2 in an animal, said method comprising the step of systemically introducing into said animal a structure comprising an antisense thrombospondin 2 consisting of a nucleic acid antisense nucleic acid that hybridizes to SEQ ID NO:3, where no guidance is taught.

Verma et al. (Nature, 1997 Vol. 389:239-242) teach the problems of gene delivery in whole organisms suffer from limitations relating to poor efficiency of delivery and the transient expression of delivered genes (page 239, second paragraph from the end).

Furthermore, Rosenberg et al. [U.S. Patent No: 5,593,974] also demonstrate the unpredictability of antisense-based therapeutics. Rosenberg et al. state, "while antisense oligonucleotides have been shown to be capable of interfering selectively with protein synthesis, and significant progress has been made on improving their intracellular stability, the problem remains that oligonucleotides must reach their intended intracellular site of action in the body in order to be effective. Where the intended therapeutic effect is a systemic one, oligonucleotides may be administered systemically. However, when it is necessary or desirable to administer the oligonucleotide to a specific region within the body, systemic administration typically will be unsatisfactory" (see column 2, lines 5-15).

As argued in the previous Office Actions, filed January 31, 2003, and October 23, 2003 there is considerable unpredictability in using antisense nucleic acid *in vivo*.

In view of the unpredictability in the art, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention over the scope claimed without having to engage in trial and error or undue experimentation. The specification as filed contemplates a method of decreasing the amount or biological activity of thrombospondin 2 in an animal, said method comprising the step of systemically introducing into said animal a structure comprising an antisense thrombospondin 2 consisting of a nucleic acid antisense nucleic acid that hybridizes to SEQ ID NO:3. The specification goes on to contemplate wherein the antisense thrombospondin 2 nucleic acid

molecule is at least 90% identical to the complement of the nucleic acid molecule of SEQ ID NO:3. The specification teaches methodologies for locally delivering an antisense thrombospondin 2 nucleic acid molecule, 100% identical to the complement of SEQ ID NO:3, to a mammalian subject, by incorporating the antisense nucleic acid molecule into the surface layer of an implanted collagen matrix device and improving vascularization of the foreign bodies that forms around the implanted device. As discussed in the previous Office Action, undue experimentation would be required of a person of skill in the art to make and use the claimed invention over the scope claimed. The quantity of experimentation required to practice the invention over the scope claimed would include the sufficient systemic delivery of a thrombospondin 2 antisense nucleic acid to specific intracellular targets in quantities sufficient to decrease thrombospondin 2 biological activity in an animal. Therefore, undue experimentation would be required of a person of skill in the art to make and use the claimed invention, particularly, in view of the obstacles needed to overcome to use antisense therapy methods as exemplified in the references discussed in the previous Office Action, and Rosenberg et al. above.

The specification does not provide particular guidance or particular direction a method of decreasing the amount or biological activity of thrombospondin 2 in an animal, said method comprising the step of systemically introducing into said animal a structure comprising an antisense thrombospondin 2 consisting of a nucleic acid antisense nucleic acid that hybridizes to SEQ ID NO:3. Further, the specification does not provide guidance to the structure and/or physical properties of an antisense thrombospondin 2 nucleic acid molecule that is at least 90% identical to the complement of the nucleic acid molecule of SEQ ID NO:3, that decreases

thrombospondin 2 activity (see 112 fist paragraph written description rejection against claim 34 below). While the specification provides guidance to locally delivering an antisense thrombospondin 2 nucleic acid molecule to a mammalian subject, by incorporating the antisense nucleic acid molecules into an implanted collagen matrix device and improving vascularization of the foreign body that forms around the implanted device, the specification provides no particular guidance of systemically delivering an antisense thrombospondin 2 nucleic acid molecule to a mammalian subject, by incorporating the antisense nucleic acid molecules into surface. Further, the specification is so broad to include the introduction of antisense thrombospondin nucleic acid molecules [plural], where it is unpredictable in the art to use even a single antisense *in vivo*.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate with the full scope of the claims. Due to the lack of specific guidance in the specification as filed and the unpredictability of using systemic gene delivery in a whole organism due to poor efficiency of delivery and the transient expression of delivered genes, one of skill in the art would require specific guidance to practice the current invention. The current specification does not provide such guidance to a method of decreasing the amount or biological activity of thrombospondin 2 in an animal comprising the implantation of a structure comprising an antisense thrombospondin 2 consisting of a nucleic acid antisense nucleic acid that hybridizes to SEQ ID NO:3, wherein the structure is a vascular graft, a vascular stent, an artificial blood vessel, an artificial bone joint, a biosensor, and a percutaneous device,

and wherein the antisense thrombospondin 2 nucleic acid molecule is at least 90% identical to the complement of the nucleic acid molecule of SEQ ID NO:3, and one of skill in the art would be required to perform trial and error or undue experimentation. The quantity of experimentation required to practice the invention over the scope claimed would include the sufficient systemic delivery of a thrombospondin 2 antisense nucleic acid to specific intracellular targets in quantities sufficient to decrease thrombospondin 2 biological activity in an animal, using a vascular graft, a vascular stent, an artificial blood vessel, an artificial bone joint, a biosensor, or a percutaneous device. Further, the quantity of experimentation required to practice the invention over the scope claimed would include the de novo determination of those antisense thrombospondin 2 nucleic acid molecules that are at least 90% identical to the complement of the nucleic acid molecule of SEQ ID NO:3, that decrease thrombospondin 2 biological activity. Therefore, undue experimentation would be required of a person of skill in the art to make and use the claimed invention.

Applicant's amendment necessitated the new ground(s) of rejection presented below:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 34 is drawn to a method for decreasing the biological activity of thrombospondin 2 in an animal, the method comprising the administration of an antisense thrombospondin 2 nucleic acid molecule that hybridizes to a nucleic acid of SEQ ID NO:3, wherein the antisense thrombospondin 2 nucleic acid molecule is at least 90% identical to the complement of the nucleic acid molecule set forth in SEQ ID NO:3.

The claimed invention encompasses antisense thrombospondin 2 nucleic acid molecules that are at least 90% identical to the complement of the nucleic acid molecule set forth in SEQ ID NO:3. The specification as filed provides only a description of the thrombospondin 2 gene (SEQ ID NO:3). The issue is that the instant Specification has not disclosed the structure or physical properties of antisense thrombospondin 2 nucleic acid molecules that are at least 90% identical to the complement of the nucleic acid molecule set forth in SEQ ID NO:3 that decrease the biological activity of thrombospondin 2 as recited in claim 34. The specification as filed, does not provide sufficient description that would allow one of skill in the art to use SEQ ID NO:3 to predict the structures any/all antisense thrombospondin 2 nucleic acid molecules that are at least 90% identical to the complement of the nucleic acid molecule set forth in SEQ ID NO:3 that decrease the biological activity of thrombospondin.

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification

must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

Additionally, "[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence."

Applicant's specification does not provide a sufficient number of representative species of antisense thrombospondin 2 nucleic acid molecules that are at least 90% identical to the complement of the nucleic acid molecule set forth in SEQ ID NO:3, which would allow one of

skill in the art to predict the structures of all members of the claimed genus of compounds. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Conclusions

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
April 7, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER